Learn More:

- About Oral Mucositis
- About Kepivance®
  - Description
  - Mechanism of Action
  - Pharmacokinetics
  - Efficacy
  - Safety & Tolerability
  - Dosing
  - Preparation & Storage
  - Frequently Asked Questions
- Tools and Resources
- For Nurses
- For Pharmacists
- Important Product Safety Information

# Efficacy

A phase III randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of Kepivance® in reducing the incidence and duration of severe oral mucositis and certain sequelae (including mouth and throat soreness, and opioid analgesic use) in patients with hematologic malignancies who were undergoing autologous PBPC transplantation after receiving TBI and high-dose CT.[1]

Video

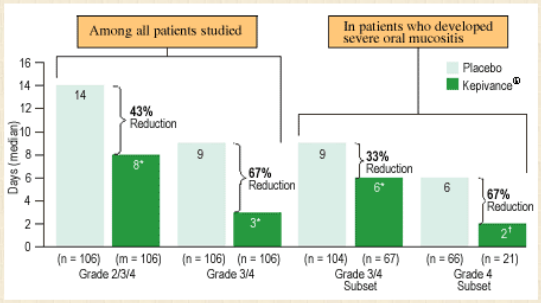
Watch a Biological Video online...

Eligible subjects were randomized (stratified by center and type of hematologic malignancy) in a 1:1 ratio to receive Kepivance® 60 mcg/kg/d or placebo for 3 consecutive days, starting 3 days before the conditioning regimen. After the conditioning regimen, patients received 3 additional doses starting on the day of stem cell infusion.[1]

## Duration of Oral Mucositis

Kepivance® resulted in a statistically significant and clinically meaningful improvement in the duration of severe oral mucositis. The primary endpoint for this study, the number of days that World Health Organization (WHO) Grade 3/4 oral mucositis occurred in the total patient population, was reduced by 67% in response to Kepivance®: median (range) was 3.0 (0, 22) days in the Kepivance® group and 9.0 (0, 27) days in the placebo group, $P < 0.001$ (Figure 1). Kepivance® also reduced the duration of Grade 3/4 oral mucositis by 33% in patients who developed this severity (median [range] of days in the Kepivance® group 6.0 [1, 22]; in the placebo group 9.0 [1, 27], $P < 0.001$).[1]

**Figure 1.** Duration of Oral Mucositis[1,2]




Adapted from Kepivance® prescribing information and Spielberger et al. *N Eng J Med.* 2004;351:2590-2598. Results from a randomized, double-blind, placebo-controlled, phase 3 study (N = 212) in which patients with hematologic malignancies who were undergoing HSCT after myelotoxic therapy received either Kepivance® or placebo. Analyses were performed in the overall patient population (patients who did not experience the event were assigned a duration of 0 days), and in subsets of patients who developed Grade 3/4 or Grade 4 oral mucositis.[1,2]

*$P < 0.001$.[1]

†$P = 0.004$.[1]

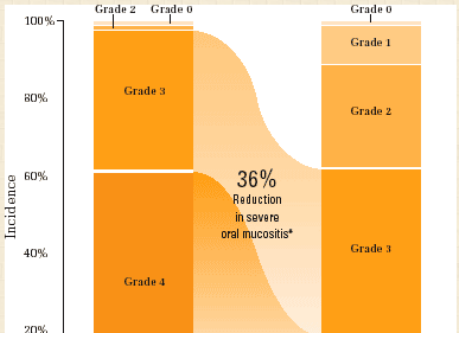
The effect of Kepivance® on the primary endpoint was further supported by the assessment of oral mucositis by the RTOG and WCCNR scales. Subjects in the Kepivance® group experienced a statistically significantly shorter duration of severe RTOG Grade 3/4 oral mucositis: median (range) was 0.0 (0, 24) days in the Kepivance® group compared with 6.0 (0, 54) days in the placebo group ($P < 0.001$).[1] A significantly shorter duration of WCCNR Grade 2/3 oral mucositis was also observed in the Kepivance® group: median (range) was 1.0 (0, 36) days in the Kepivance® group versus 7.0 (0, 56) days in the placebo group ($P < 0.001$). In all patients studied, the duration of WHO Grade 2/3/4 oral mucositis was statistically significantly shorter for patients in the Kepivance® group: median (range) was 8.0 (0, 28) days in the Kepivance® group compared with 14.0 (0, 37) days in the placebo group ($P < 0.001$), representing a 43% reduction in duration of WHO Grade 2/3/4 in response to Kepivance®.[1]

Back to top

## Incidence of Severe Oral Mucositis

Kepivance®(palifermin) significantly reduced the incidence of severe grades of oral mucositis shifting to milder grades (Figure 2). The incidence of WHO Grade 3/4 oral mucositis was 63% in the Kepivance® group compared with 98% in the placebo group ($P < 0.001$).[1]

**Figure 2.** Oral Mucositis Incidence (All WHO Grades)[1,2]

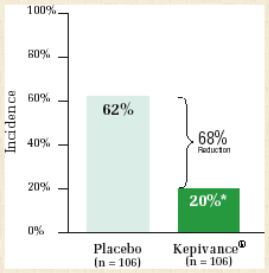



Adapted from Kepivance® prescribing information.
*$P < 0.001$. Results from a randomized, double-blind, placebo-controlled, phase 3 study (N = 212) in which patients with hematologic malignancies who were undergoing HSCT after myelotoxic therapy received either Kepivance® or placebo.[1,2]

▲ Back to top

A further significant reduction in the incidence of the most severe form of oral mucositis (WHO Grade 4) was observed: incidence of WHO Grade 4 in the Kepivance® group was 20% compared with 62% for placebo, $P < 0.001$ (Figure 3).[1]

**Figure 3.** Incidence of WHO Grade 4 Mucositis[1]

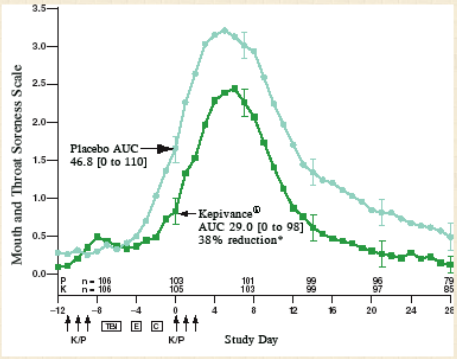



Adapted from Spielberger, et al. *N Engl J Med*. 2004;351:2590-2598.
*$P < 0.001$.

## Impact of Kepivance® On Patient-Reported Outcomes (PRO) and Associated Measures

The effect of Kepivance® on PRO measurements, including mouth and throat soreness and related functional activities (eating, drinking, swallowing, and talking), was consistent with the clinical findings in that significant improvement was reported. The area under the curve (AUC) for mouth and throat soreness (Figure 4), with smaller AUC values indicating improvement, showed a statistically significant benefit with Kepivance®. Median (range) AUC in the Kepivance® group was 29.0 (0, 98) compared with 46.8 (0, 110) in the placebo group ($P < 0.001$), representing a 38% reduction in mouth and throat soreness for patients who received Kepivance®.[1] The AUC for mouth and throat soreness was based on a scale with 5 response categories from 0 (no soreness) to 4 (extreme soreness). The impact of this decrease in mouth and throat soreness on related functional activities was evaluated to determine if Kepivance® resulted in an improvement in the abilities to eat, drink, swallow, and talk.[1,3]

**Figure 4.** Patient Reported Outcome: Mouth and Throat Soreness[1]




Adapted from Spielberger, et al. *N Engl J Med*. 2004;351:2590-2598.
*$P < 0.001$.
K/P = Kepivance® or Placebo
TBI = Total-Body irradiation
E = Etoposide
C = Cyclophosphamide
PBPC = Peripheral blood progenitor cell

▲ Back to top

A daily diary was used to evaluate functional activities related to a patient's mouth and throat soreness: eating, drinking, swallowing, and talking. Swallowing scores showed a lower mean score for the Kepivance® group, indicating better performance: mean AUC for the Kepivance® group 22.5, and for the placebo group 38.3 ($P < 0.001$), representing a 38% improvement in swallowing ability.[1] Results for other daily functions assessed were similar in that all related functions improved significantly (Table 1, $P < 0.001$). Kepivance® patients reported significant improvement in eating, drinking, and talking compared with placebo-treated patients: eating 40%; drinking 38%; talking 47% ($P < 0.001$).[1,3] These data indicate that functional activities related to the mouth and throat soreness improved significantly in Kepivance® patients.

**Table 1.** Effect of Kepivance® (palifermin) on Functional Daily Activities Assessed by Patient-Reported Outcomes[1,3]

| Patient-Reported Outcome | % Improvement Kepivance® vs Placebo |
|---|---|
| Mouth and throat soreness | 38%* |

| | |
|---|---|
| Eating | 40%* |
| Swallowing | 38%* |
| Drinking | 38%* |
| Talking | 47%* |

Adapted from Spielberger et al. *N Engl J Med.* 2004;351:2590-2598 and Spielberger et al. *J Support Oncol.* 2004;2(suppl 2):73-74.
*$P < 0.001$. Results from a randomized, double-blind, placebo-controlled, phase 3 study (N = 212) in which patients with hematologic malignancies who were undergoing HSCT after myelotoxic therapy received either Kepivance® or placebo. Mouth and throat soreness (MTS) and functional activity scores were collected with the use of a daily questionnaire and measured using a 5-point scale. MTS was a prespecified endpoint. Other functional activities were planned analyses.[1]

▲ Back to top

Kepivance® helps reduce the downstream clinical consequences as well (Table 2).[1,2]

**Table 2.** Clinical Consequences of Severe Oral Mucositis[1,2]

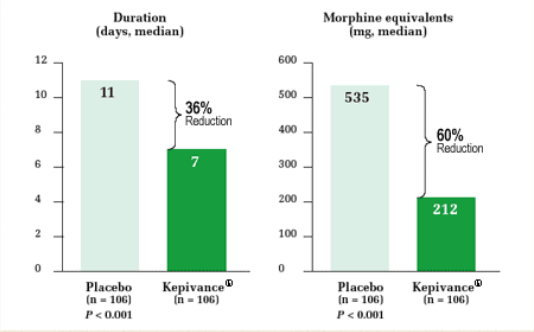
| Severe Oral Mucositis Consequences | Placebo (n = 106) | Kepivance® (n = 106) | Reduction with Kepivance® | *P* - Value |
|---|---|---|---|---|
| Median days of opioid use | 11.0 | 7.0 | 4 days | $P < 0.001$ |
| Incidence of TPN | 55% | 31% | 44% | $P < 0.001$ |

Adapted from Spielberger et al. *N Engl J Med.* 2004;351:2590-2598.
* Results from a randomized, double-blind, placebo-controlled, phase 3 study (N = 212) in which patients with hematologic malignancies who were undergoing HSCT after myelotoxic therapy received either Kepivance® or placebo. Opioid use was a prespecified endpoint. Incidence of TPN was a planned analysis and was given according to the standards of each study site.[1,2]

▲ Back to top

Consistent with the decrease in mouth and throat soreness, statistically significant decreases in the duration of use and median cumulative dose of parenteral opioid analgesics (mg morphine equivalents) were also observed in the Kepivance® group compared with placebo (Figure 5). The duration of opioid analgesic use was: median (range) 7.0 (0, 28) days in the Kepivance® group and 11.0 (0, 32) days for placebo, representing a 36% reduction ($P < 0.001$) in duration of use of analgesics following administration of Kepivance®. The median (range) cumulative dose of opioid analgesics administered was 212 (0, 9418) mg in the Kepivance® group and 535 (0,9418) mg in the placebo group ($P < 0.001$), representing a 60% reduction in dose required in the Kepivance® patients.[1]

**Figure 5.** Parenteral Opioid Analgesic Use[1,2]

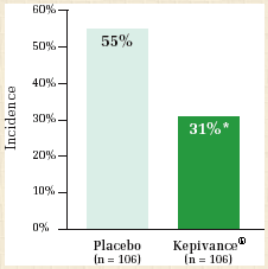



Adapted from Spielberger et al. *N Engl J Med.* 2004;351:2590-2598 and Kepivance® PI, 2004.
Results from a randomized, double-blind, placebo-controlled, phase 3 study (N = 212) in which patients with hematologic malignancies who were undergoing HSCT after myelotoxic therapy received either Kepivance® or placebo.[1]

▲ Back to top

Kepivance® also significantly reduced the need for TPN: incidence in the Kepivance® group was 31% as compared with 55% for placebo (Figure 6, $P < 0.001$).[1]

**Figure 6.** Incidence of TPN[1]




Adapted from Spielberger et al. *N Engl J Med.* 2004;351:2590-2598.
*$P < 0.001$. Results from a randomized, double-blind, placebo-controlled, phase 3 study (N = 212) in which patients with hematologic malignancies who were undergoing HSCT after myelotoxic therapy received either Kepivance® or placebo. Incidence of TPN was a planned analysis and was given according to the standards of each study site.[1,2]

There was no evidence of a delay in time to hematopoietic recovery in patients who received Kepivance® as compared to patients who received placebo. In clinical trials, patients undergoing myeloablative therapy routinely received granulocyte colony-stimulating factor (G-CSF) following PBPC infusion, and there was no apparent difference in neutrophil recovery between patients receiving Kepivance® and those receiving placebo.[2]

## Summary

This clinical trial demonstrated that patients receiving Kepivance® had a clinically and statistically significant reduction in the number of days they experienced severe oral mucositis (WHO Grade 3/4), compared with patients receiving placebo. Furthermore, Kepivance® was associated with clinically meaningful and statistically significant improvements in the requirement for opioid analgesics for oral mucositis; patient-reported mouth and throat soreness and associated sequelae; and the requirement for TPN.[1,2] These findings collectively demonstrate the value of Kepivance® in reducing the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring HSCT.

Kepivance® is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. The safety and efficacy of Kepivance® have not been established in patients with non-hematologic malignancies.

### Important Safety Information

In patients with hematologic malignancies, the most common serious adverse reaction in clinical trials attributed to Kepivance® was skin rash reported in less than 1% of patients. Other serious adverse reactions occurred at a similar rate in patients who received Kepivance® or placebo with the most frequent being fever, gastrointestinal events, and respiratory events. The most commonly reported adverse reactions attributed to Kepivance® were rash, erythema, edema, pruritus, dysesthesia, mouth/tongue thickness/discoloration, and taste alteration.


[1] Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. 2004;351:2590-2598.

[2] Kepivance® (palifermin) prescribing information.

[3] Spielberger R, Emmanouilides C, Stiff P, et al. Use of recombinant human keratinocyte growth factor (palifermin) can reduce severe oral mucositis in patients with hematologic malignancies undergoing autologous peripheral blood progenitor cell transplantation after radiation-based conditioning. *J Support Oncol*. 2004;2(suppl 2):73-74.



▲ Back to top

ABOUT ORAL MUCOSITIS
ABOUT KEPIVANCE®
TOOLS AND RESOURCES
FOR NURSES
FOR PHARMACISTS
IMPORTANT PRODUCT SAFETY INFORMATION



Kepivance® is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. The safety and efficacy of Kepivance® have not been established in patients with non-hematologic malignancies.

### Important Safety Information

In patients with hematologic malignancies, the most common serious adverse reaction in clinical trials attributed to Kepivance® was skin rash reported in less than 1% of patients. Other serious adverse reactions occurred at a similar rate in patients who received Kepivance® or placebo with the most frequent being fever, gastrointestinal events, and respiratory events. The most commonly reported adverse reactions attributed to Kepivance® were rash, erythema, edema, pruritus, dysesthesia, mouth/tongue thickness/discoloration, and taste alteration.


biovitrum.


Contact | Reimbursement | Biovitrum.com | Site Map

Prescribing Information